

Negative symptoms and cognitive functioning in ARMS

**The relationship between negative symptoms and cognitive functioning in patients with an at-risk mental state for psychosis**

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### **Abstract**

Negative symptoms and neurocognitive performance have been reported to be negatively associated in patients with emerging psychosis. However, most previous studies focused on patients with frank psychosis and did not differentiate between subdomains of negative symptoms. Hence, we aimed to elucidate the specific relationship between negative symptoms and cognitive functioning in patients with an at-risk mental state (ARMS) for psychosis. Data from 154 ARMS patients collected within the prospective Früherkennung von Psychosen (FePsy) study were analysed. Negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms (SANS) and cognitive functioning with an extensive neuropsychological test battery. Regression analyses revealed significant negative associations between negative symptoms and cognitive functioning, particularly in the domains of nonverbal intelligence and verbal fluency. When analyzing each negative symptom domain separately, alogia and asociality/anhedonia were significantly negatively associated with nonverbal intelligence and alogia additionally with verbal fluency. Overall, our results in ARMS patients are similar to those reported in patients with frank psychosis. The strong negative association between verbal fluency and negative symptoms may be indicative of an overlap between these constructs. Verbal fluency might have a strong influence on the clinical impression of negative symptoms (particularly alogia) and vice versa.

### 1. Introduction

Early detection and intervention in patients with an at-risk mental state for psychosis (ARMS) represents a growing and promising field of research (Riecher-Rössler and McGorry, 2016; Riecher-Rössler and Studerus, 2017). ARMS patients are exposed to a high risk of developing frank psychosis, with transition risks up to 36% after 3 years of follow-up (Fusar-Poli et al., 2012a). Previous studies showed that not only positive psychotic symptoms such as hallucinations, delusions and thought disorders, but also negative symptoms (Cotter et al., 2014) and cognitive impairments (for meta-analysis see Hauser et al., 2017) are frequently present in ARMS patients.

Negative symptoms have previously been identified as a central clinical feature of psychosis (for review see Strauss and Cohen, 2017). Currently, the distinction of 5 negative symptom domains, namely blunted affect, alogia, asociality, avolition and anhedonia has become widely accepted (Strauss and Cohen, 2017). Negative symptoms are already present in ARMS patients and patients with a first-episode psychosis (FEP) and several studies highlighted their importance regarding the outcome of these patient groups. More severe negative symptoms are related to poorer social and role functioning in ARMS (Carrión et al., 2016; Cotter et al., 2014) and FEP patients (Diaz-Caneja et al., 2015), and negative symptoms represent significant predictors for conversion to psychosis (Demjaha et al., 2012; Piskulic et al., 2012; Riecher-Rössler et al., 2009; Valmaggia et al., 2013).

Apart from positive and negative symptoms, cognitive impairments are regarded as a core feature of psychosis and are present in a considerable number of ARMS and FEP patients (Hauser et al., 2017). Although less severe than in FEP patients, ARMS patients show significant and widespread impairments in different domains of cognitive functioning such as general intelligence, attention/vigilance, verbal learning, visual learning, social cognition, executive functioning, processing speed, verbal fluency, working memory and verbal and visual memory (Fusar-Poli et al., 2012b; Hauser et al., 2017). It has been shown that ARMS patients with later transition to psychosis perform significantly worse in cognitive tasks than patients without later transition in nearly all cognitive domains (Hauser et al., 2017; Riecher-Rössler and Studerus, 2017; Studerus et al., 2016). In longitudinal studies, cognitive impairments at baseline predicted poor social, role and occupational outcome (Cotter et al., 2014).

So far, many studies have focused on associations between negative symptoms and cognitive functioning in FEP patients and/or individuals with a lifetime history of psychosis (de Gracia Dominguez et al., 2009). A systematic review of 58 studies (5009 individuals) found that higher levels of negative symptoms were modestly associated with lower cognitive functioning (correlations from  $-.29$  to  $-.12$ ), with the highest correlation between negative

symptoms and verbal fluency. In contrast, positive psychotic symptoms were not significantly associated with cognition (de Gracia Dominguez et al., 2009). So far, only few studies have investigated the association between negative symptoms and cognitive functioning in ARMS patients and those that exist have found similar results as in FEP patients. Specifically, higher levels of negative symptoms were associated with slower processing speed and poorer performance on verbal tasks involving verbal learning and memory or verbal fluency (Lindgren et al., 2010; Meyer et al., 2014), lower performance accuracy (Gur et al., 2015), poorer executive functioning, vigilance and problem solving (Meyer et al., 2014) and a general poorer performance in neurocognitive functioning (Gur et al., 2015; Meyer et al., 2014). However, the majority of these studies included relatively small sample sizes or did not differentiate between the above mentioned five negative symptom domains.

Hence, the aim of this study was to evaluate the relationship between negative symptoms and cognitive functioning in ARMS patients, analyzing each negative symptom domain separately.

We hypothesized, that worse neurocognitive performance would be associated with a higher level of negative but not positive psychotic symptoms in ARMS patients. Based on the findings reported in FEP patients (de Gracia Dominguez et al., 2009), we expected to find the strongest associations between negative symptoms and verbal fluency tasks.

## **2. Methods**

### **2.1 Setting and Recruitment**

The data analysed in this study were collected within the prospective *Früherkennung von Psychosen* (FePsy; early detection of psychosis) study, which aims to improve early detection of psychosis (Riecher-Rössler et al., 2007; Riecher-Rössler et al., 2009). Patients were recruited via the FePsy Clinic, University of Basel Psychiatric Hospital Basel, Switzerland, which was set up specifically to identify, assess, and treat individuals in the early stages of psychosis. All patients were recruited between April 2000 and August 2015. The study was approved by the ethics committee of North-western and Central Switzerland (EKNZ) and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

### **2.2 Screening Procedure**

ARMS patients were identified using the Basel Screening Instrument for Psychosis (BSIP), which was developed by Riecher-Rössler et al. (2008). The BSIP allows the rating of individuals regarding the inclusion/exclusion criteria corresponding to the Personal Assessment and Crisis Evaluation (PACE) criteria by Yung et al. (1998) and has been shown to have a high predictive validity (Riecher-Rössler et al., 2008; Riecher-Rössler et al., 2009).

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Exclusion criteria were age <18, insufficient knowledge of German, IQ <70, previous episode of schizophrenic psychosis (treated with antipsychotics for >3 weeks (lifetime) and/or a total amount of  $\geq 2500$ mg chlorpromazine equivalent), psychosis clearly due to organic reasons or substance abuse, or psychotic symptoms within a clearly diagnosed affective psychosis or borderline personality disorder (Riecher-Rössler et al., 2007).

### **2.3 Psychopathological Assessments**

Negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1989). Variables used in statistical analyses were the SANS total score and its five original subscales (i.e., affective flattening, alogia, avolition/apathy, asociality/anhedonia and inattention). Positive psychotic symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS; Ventura et al., 1993). For statistical analyses we used the factor psychosis of the BPRS four-factor structure proposed by Velligan et al. (2005).

### **2.4 Neurocognitive Assessment**

We used a neuropsychological test battery which was mainly based on computer-administered tests. The domains and tests included were as follows: General intelligence was assessed using the Mehrfachwahl-Wortschatz-Test (MWT-A; Lehrl, 1991) and the Leistungsprüfungssystem, scale 3 (LPS; Horn, 1983). Both tests are well-established German intelligence scales for estimating verbal (MWT-A) and non-verbal (LPS) abilities (i.e., abstract reasoning). Planning ability was evaluated with the Tower of Hanoi (ToH; Gediga and Schöttke, 1994), cognitive flexibility with the Wisconsin Card Sorting Test (WCST; Drühe-Wienholt and Wienholt, 1998), selective attention and reaction inhibition with the Go/No-Go subtest of the Test of Attentional Performance (TAP; Zimmermann and Fimm, 1993). Working memory was measured with the TAP working memory (WM) subtest (Zimmermann and Fimm, 1993), verbal learning and memory with the California Verbal Learning Test (CVLT; Delis et al., 1987) and verbal fluency with the Verbal Fluency Test (VF), which is based on the German Regensburger Wortflüssigkeits-Test (RWT; Aschenbrenner et al., 2000). Since the latter was only introduced into the FePsy study design in 2013, it was only obtained in a small subset of the included ARMS patients. Attention was assessed with the Continuous Performance Test (CPT-OX; Rosvold et al., 1956), which in a stricter sense measures vigilance. For a more detailed description of the above mentioned tests, see Rapp et al. (2013) or Pflueger et al. (2007).

## 2.5 Statistical Analyses

All statistical analyses were conducted using the IBM Statistical Package for the Social Sciences Version 22.0 (IBM Corp., 2013) and the R environment for statistical computing (R Core Team, 2016).

We applied various transformations to variables of the SANS, the BPRS and the neuropsychological test battery that did not conform to assumptions of normality (see Supplementary Table 1). Additionally, some neuropsychological variables were recoded, such that a higher score always indicated a better performance. To reduce statistical analyses, composite scores were calculated for each subtest of the neuropsychological test battery in accordance with other studies (Lewandowski et al., 2011; Rapp et al., 2013). All composite scores were the average of the z-transformed performance scores and were only included in further analyses, if their internal consistency reached a minimum Cronbach's  $\alpha$  of .7, as suggested in Field (2013). Following this guideline, composite scores were obtained for ToH ( $\alpha = .88$ ), WCST ( $\alpha = .86$ ), CVLT ( $\alpha = .76$ ) and VF ( $\alpha = .78$ ). Measures of overall reliability for TAP Go/No-Go ( $\alpha = .34$ ), TAP-WM ( $\alpha = .50$ ), CPT ( $\alpha = .20$ ), and IQ ( $\alpha = .46$ ) did not reach satisfying levels. Therefore, composite scores of TAP Go/No-Go, TAP-WM and CPT were replaced with the measure of sensitivity called *d prime* ( $d'$ ;  $d'$ -TAP Go/No-Go,  $d'$ -TAP WM and  $d'$ -CPT), which takes both hits and false alarms into account by calculating the relative proportion of those components in a task (Haatveit et al., 2010). To generate normal distribution, some  $d'$  variables were subsequently transformed (see Supplementary Table 1). For IQ, the single variables of verbal (MWT-A IQ) and non-verbal (LPS IQ) intelligence were used for further statistical analyses instead of the composite score.

Multiple linear regression models were fitted to explore the relationship between negative symptoms and neurocognition. Cognitive variables such as composite scores,  $d'$  variables and the two IQ measures served as independent variables, the SANS total score and the BPRS psychosis factor were entered as dependent variables. Separate linear regression models were fitted for each cognitive composite score and dependent variable. The different subscales of negative symptoms were only further analyzed if a significant result emerged regarding the SANS total score. Age and gender were included as covariates in all models. Testing was two-tailed at a 5% significance level and missing values were excluded listwise. To account for multiple testing, corrected  $p$ -values were calculated separately for the SANS total score and for each negative symptom subscale using the false discovery rate (Benjamini and Hochberg, 1995).

## 3. Results

In total, data of 154 ARMS patients who met the requested inclusion criteria were analyzed. 11 patients did take antipsychotic medication, which however did not exceed a total

cumulative lifetime dose of 2500 mg of chlorpromazine equivalents. Sociodemographic and clinical sample characteristics are presented in Table 1.

- Insert Table 1 about here -

### 3.1 Regression analyses

Detailed information of multiple linear regression analyses for SANS total score can be found in Table 2. After correction for multiple testing, regression analyses revealed significant negative associations between SANS total score and verbal fluency as well as with non-verbal IQ, whereby verbal fluency showed the strongest negative association. Multiple regression models including the BPRS psychosis factor as dependent variable revealed that no cognitive variable was significantly associated with positive psychotic symptoms of the BPRS.

- Insert Table 2 about here -

The following results emerged when the SANS subscales were further analysed:

- *Alogia* was significantly associated with both nonverbal IQ ( $p = .024$ ) and verbal fluency ( $p = .024$ ).
- *Asociality/Anhedonia* was significantly associated with nonverbal IQ ( $p = .023$ ).

The subscales Affective Flattening, Avolition/Apathy and Inattention did not withstand correction for multiple testing. Information on the associations between neurocognitive domains and psychopathological symptoms corrected for multiple testing is summarized in the heat map (see Figure 1).

- Insert Figure 1 about here -

## 4. Discussion

The aim of this study was to investigate the relationship between negative symptoms and cognitive functioning in a sample of 154 ARMS patients, analyzing each negative symptom domain separately. In accordance with our hypothesis, we found that patients suffering from more severe negative symptoms performed worse in most neurocognitive tasks, while frank positive psychotic symptoms were not significantly associated with cognitive performance. These results are consistent with most previous studies investigating the associations

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between psychopathological symptoms and cognitive functioning in ARMS (Gur et al., 2015; Lindgren et al., 2010; Meyer et al., 2014) and FEP patients (de Gracia Dominguez et al., 2009). However, not all performed studies have found associations between negative symptoms and cognitive deficits among ARMS patients (Kim et al., 2011; Niendam et al., 2006; Ohmuro et al., 2015; Pukrop et al., 2007). This might be due to the rather small sample sizes in those studies. In addition, Niendam et al. (2006) made use of the conservative Bonferroni correction. However, the associations observed by Niendam et al. (2006) and Ohmuro et al. (2015) showed the same pattern as in studies reporting significant associations.

When we corrected our analyses for multiple testing, the strongest association was found between negative symptoms and verbal fluency, with a higher SANS total score associated with reduced verbal fluency. This result is in line with our hypothesis and matches the results reported in FEP patients (de Gracia Dominguez et al., 2009). Verbal fluency seems to be impaired already in the early stages of emerging psychosis and has previously been suggested as a possible predictor for transition to psychosis (Addington et al., 2017; Becker et al., 2010; Hauser et al., 2017). Furthermore, studies have indicated that ARMS and FEP patients show reduced activation in the anterior cingulate gyrus (Fu et al., 2005; Fusar-Poli et al., 2011; Schaufelberger et al., 2005), the inferior frontal cortex and the inferior prefrontal cortex (Fu et al., 2005; Schaufelberger et al., 2005) when performing verbal fluency tasks. As other studies in ARMS (Fornito et al., 2008) and patients with schizophrenic psychoses (Bersani et al., 2014) have shown, cingulate regions seem not only to be linked to verbal fluency, but also to negative symptoms. It might be speculated that this association points to similar pathogenic pathways of negative symptoms and verbal fluency deficits.

Alternatively, the association found between verbal fluency and negative symptoms may be indicative of an overlap between these constructs. When the SANS negative symptom subscales were investigated separately, verbal fluency was only found to be associated with the alogia subscale. Thus, it could be suspected that an impaired verbal fluency leads to the clinical impression of alogia. Vice versa, it seems logical that patients suffering from alogia show lower cognitive performance in tasks involving verbal fluency. Thus it might be possible that some of the associations found in this study might be explained by a construct overlap.

We used the SANS for the assessment of negative symptoms, an instrument that has previously been criticized for the inclusion of inattentiveness, which per se measures cognition rather than negative symptoms (Lincoln et al., 2016), and represents a further area of construct overlap. Recent studies have pointed out that the conceptualization of negative symptoms has changed over the years (Blanchard et al., 2011) and efforts have been made to develop new assessment instruments such as the Clinical Assessment Interview for

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Negative Symptoms (CAINS; Kring et al., 2013) and the Brief Negative Symptom Scale (BNSS; Kirkpatrick et al., 2011), which are both based on this new conceptualization (see Carpenter et al., 2016; Lincoln et al., 2016 for review). Thus, future studies should use these novel scales when assessing negative symptoms, as they allow for a clearer distinction between negative symptoms and cognition.

After correction for multiple testing also the association between negative symptoms and nonverbal intelligence remained significant, with increasing negative symptoms being associated with lower nonverbal IQ. Here, nonverbal intelligence was significantly associated with 2 out of 5 negative symptom subscales (i.e., alogia and asociality/anhedonia). Earlier studies have reported significant associations between full-scale IQ and negative symptoms in patients with affective and non-affective psychoses (de Gracia Dominguez et al., 2009; Kravariti et al., 2012) and in patients with schizophrenic psychoses (Basso et al., 1998). However, studies explicitly analyzing associations of *nonverbal* intelligence with negative symptom *subscales* are lacking so far. Also, such studies have not yet been published for ARMS patients. Thus, to the best of our knowledge, this is the first study to analyze this specific relationship in ARMS patients, indicating that nonverbal intelligence is more strongly associated with negative symptoms than verbal intelligence.

Some points need to be discussed regarding the direction of the association between negative symptoms and neurocognition. As data were analyzed cross-sectionally, the present findings do not implicate causality. Studies which longitudinally investigated the predictive relationship of cognitive functioning and negative symptoms in FEP patients and individuals with schizophrenic psychoses found inconsistent results. For example, Lipkovich et al. (2009) found that processing speed affected psychosocial functioning directly and indirectly via negative symptoms at a 6-week follow-up. Schüpbach et al. (2007) reported that an early improvement of negative symptoms predicted better neurocognitive performance at a 2-year follow-up. Nevertheless, the authors also found that an early improvement of cognitive deficits was significantly associated with an improvement of both negative and positive symptoms at 2-year follow-up (Schüpbach et al., 2007). Given that cognitive deficits share a neurodevelopmental as well as a genetic component (Bora et al., 2014; Kim et al., 2011), it might be assumed that cognitive deficits develop long before negative symptoms arise. Therefore, cognitive deficits may predict the severity of negative symptoms in ARMS patients rather than the other way round.

When interpreting results associated with cognition, motivational aspects should also be taken into account. An individual's motivation may have a major impact on neuropsychological testing and results. In a recent study Moritz et al. (2017) performed mediation analyses and found that motivational deficits contributed to poorer neurocognitive performance.

#### **4.1 Strengths and Limitations**

Results obtained in this study are based on cross-sectional data only. Further analyses should focus on longitudinal data to investigate the predictive relationship between neurocognition and negative symptoms.

Strengths of our study were that we used a comparably larger sample of ARMS patients than the majority of the previous studies did, which improved the statistical power of our study. Also, we analyzed every negative symptom subscale separately to investigate the relationship of negative symptoms and cognition in a more detailed way. All results were controlled for the covariates age and gender. Only 11 out of 154 patients were treated with antipsychotic medication and results did not differ when analyses were performed with and without controlling for intake of antipsychotic medication.

#### **4.2 Conclusions**

Taken together, our results suggest that worse neurocognitive performance is associated with a higher level of negative symptoms in ARMS patients. Measures of nonverbal intelligence and verbal fluency were particularly associated with negative symptoms in this study. The strong association found between verbal fluency and negative symptoms may be indicative of an overlap between those constructs, since impaired verbal fluency might lead to the clinical impression of alogia.

Future studies should focus on a better differentiation between cognitive deficits and negative symptoms to reduce construct overlap. Furthermore, a multimodal approach incorporating neuroimaging in addition to psychopathological and neuropsychological data could provide further insights into the underlying pathogenic processes of cognitive deficits and negative symptoms. Detecting and treating these processes as early as possible in ARMS patients would assure the best possible functional outcome.

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These institutions had no further role in the study design; collection, analysis and interpretation of data; in the writing of the report and in the decision to submit the paper for publication.

**Conflict of interest**

None.

**Ethical Standards**

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

**Table 1**

Sociodemographic and clinical characteristics of included ARMS patients.

	ARMS total group (n = 154)			
	<i>n</i>	%	<i>M</i>	<i>SD</i>
Men	104	67.5%		
Women	50	32.5%		
Age			25.94	7.38
Years of education			11.62	2.88
Antipsychotics <sup>1</sup> currently				
<i>None</i>	142	92.9%		
<i>Risperidone</i>	4	2.6%		
<i>Quetiapine</i>	1	0.6%		
<i>Olanzapine</i>	6	3.9%		
Antidepressants currently	51	33.1%		
Anxiolytics currently	27	17.5%		
SANS total score			21.44	17.62
BPRS psychosis			6.17	2.59

*Note.* ARMS: At-risk mental state; SANS: Scale for the Assessment of Negative Symptoms; BPRS: Brief Psychiatric Rating Scale.

<sup>1</sup>Antipsychotics: only patients with a cumulative lifetime exposure of less than a total chlorpromazine equivalent of 2500 mg were included.

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**Table 2**

Associations between the SANS total score and performance in various neurocognitive domains.

Predictor	SANS Total score							
	n	$\beta$	T	B	SE	CI	p - value	p – value (corrected)
Verbal IQ	94	-.19	-1.74	-.22	.13	-.47 to .03	.085	.102
Non-Verbal IQ	93	-.32	-3.15	.00	.00	-.003 to -.001	.002**	.020*
Planning Ability	81	-.22	-2.01	-5.09	2.53	-10.12 to -.05	.048*	.072
Cognitive Flexibility	90	-.18	-1.71	-3.83	2.24	-8.29 to .63	.091	.102
Verbal Fluency	27	-.51	-2.86	-10.94	3.82	-18.84 to -3.04	.009**	.040*
Verbal Learning & Memory	79	-.27	-2.30	-7.30	3.17	-13.61 to -.99	.024*	.051
Selective Attention & Inhibition	92	-.23	-2.23	-6.23	2.80	-11.79 to -.68	.028*	.051
Working Memory	93	-.25	-2.42	-4.85	2.00	-8.83 to -.87	.017*	.051
Vigilance	86	.00	.02	.00	.05	-.10 to .10	.986	.986

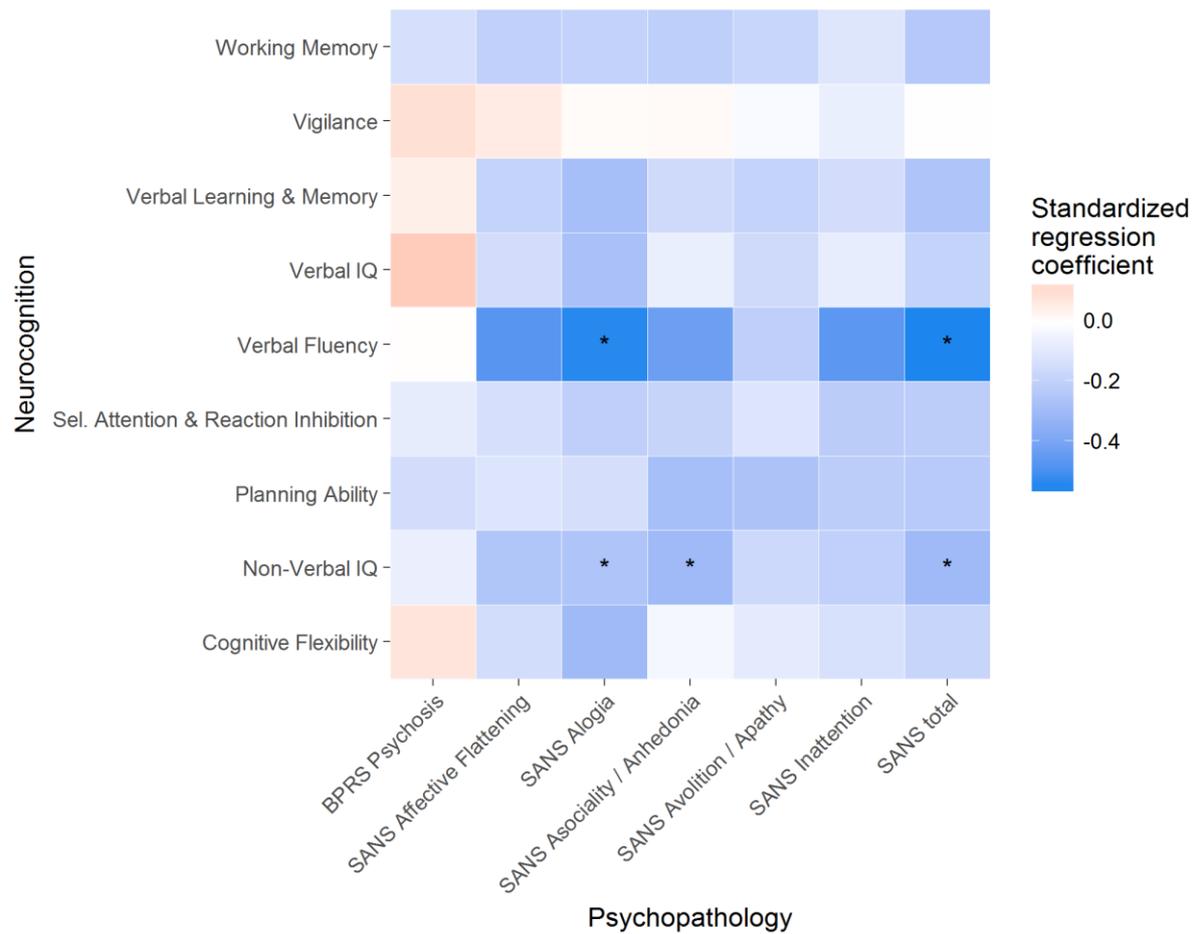
*Note.* SANS: Scale for the Assessment of Negative Symptoms; Verbal IQ: Mehrfachwahl-Wortschatz-Test (MWT-A); Non-Verbal IQ: Leistungsprüfungssystem (LPS); Planning Ability: Tower of Hanoi (ToH); Cognitive Flexibility: Wisconsin Card Sorting Test (WCST); Verbal Fluency: Verbal Fluency Test (VF); Verbal Learning and Memory: California Verbal Learning Test (CVLT); Selective Attention and Reaction Inhibition:  $d'$  of the Test of Attentional Performance, Go/No-Go subtest (TAP Go/No-Go); Working Memory:  $d'$  of the Test of Attentional Performance, Working Memory subtest (TAP-WM); Vigilance:  $d'$  of the Continuous Performance Test (CPT).

$\beta$ : standardized regression coefficient; B: unstandardized regression coefficient; SE: standard error; CI: 95% confidence interval; Each of the multiple regressions was performed with one neurocognitive predictor. The covariables age and gender are not listed.

\*  $p < .05$

\*\*  $p < .01$

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**Figure 1.** Associations between psychopathology subscales and neurocognitive domains.

*Note.* SANS: Scale for the Assessment of Negative Symptoms; BPRS: Brief Psychiatric Rating Scale.

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